COMMUNICATION

Decarboxylative Conjunctive Cross-coupling of Vinyl Boronic Esters using Metallaphotoredox Catalysis

Riccardo S. Mega, Vincent K. Duong, Adam Noble* and Varinder K. Aggarwal*

Abstract: The synthesis of complex alkyl boronic esters via a conjunctive cross-coupling of vinyl boronic esters with carboxylic acids and aryl iodides is described. The reaction proceeds under mild metallaphotoredox conditions and involves an unprecedented decarboxylative radical addition/cross-coupling cascade of vinyl boronic esters. Excellent functional group tolerance is displayed, and application of a range of carboxylic acids, namely secondary α-amino acids, and aryl iodides provides efficient access to highly functionalized alkyl boronic esters. The decarboxylative conjunctive cross-coupling was also applied to the synthesis of *sedum* alkaloids.

Reactions that can transform feedstock chemicals into structurally complex and synthetically valuable products are highly sought after in organic synthesis. An attractive approach to achieving this goal is to use multicomponent reactions, wherein three or more substrates are simultaneously coupled, thus rapidly increasing molecular complexity.[1] A useful subset of these reactions is three-component conjunctive cross-couplings of carbon–carbon π-bonds, which extends the synthetic utility of traditional cross-couplings by incorporating a conjunctive reagent that is difunctionalized by reaction with both the nucleophilic and electrophilic coupling partners (Scheme 1a).[2] Despite recent advances in this area, these methods rely heavily on organometallic reagents, prefunctionalized starting materials and precious metal catalysts.

Carboxylic acids, which are abundant feedstock chemicals, have recently emerged as unconventional alternatives to traditional nucleophilic coupling partners in cross-coupling reactions.[3] This is due to recent developments in metallaphotoredox catalysis, where carboxylic acids undergo single-electron transfer (SET)-mediated decarboxylative cross-coupling in the presence of a nickel catalyst under mild photocatalytic conditions.[4] Although metallaphotoredox catalysis has found many applications in two-component decarboxylative cross-coupling reactions,[5] extension to three-component conjunctive cross-couplings of alkenes has not been reported.[6] To date, examples of metallaphotoredox-catalyzed conjunctive cross-couplings are limited to the use of preactivated substrates, such as oxalate esters or alkyl silicates,[7] which must first be synthesized.[8] As such, the development of related reactions that utilize readily available carboxylic acids is highly desirable.

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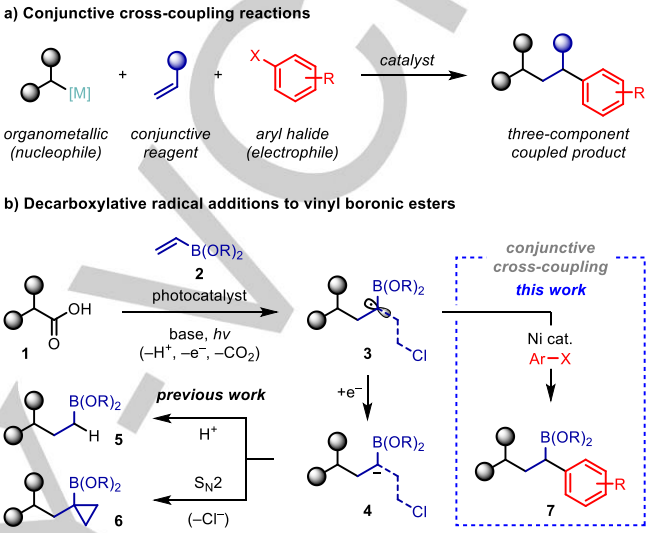
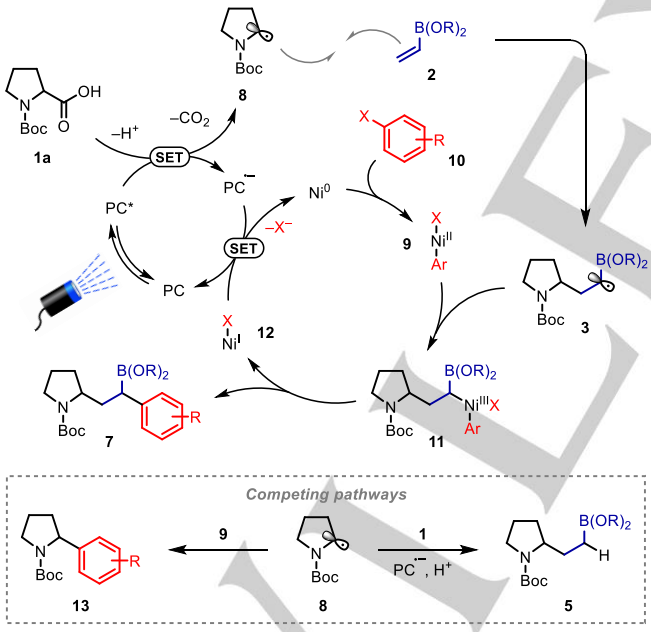


Scheme 1. Conjunctive cross-coupling reactions and decarboxylative radical additions to vinyl boronic esters.

We recently reported a photoredox-catalyzed decarboxylative Giese reaction between carboxylic acids **1** and vinyl boronic esters **2** (Scheme 1b).[9] Key to the success of this reaction was the formation of a stabilized α-boryl radical **3** upon addition of an alkyl radical to **2**. We demonstrated that radical **3** could be reduced by the photocatalyst to the corresponding anion **4**, giving the Giese product **5** after protonation. This radical–polar crossover methodology was also extended by intercepting α-boryl anion **4** in an intramolecular alkylation to access a range of boronic ester-substituted cyclopropanes **6**.[10] Inspired by recent reports of nickel catalyzed cross-couplings of α-boryl halides,[11] we questioned whether the α-boryl radical intermediate **3** could be intercepted in nickel-catalyzed cross-couplings with aryl halides to generate benzylic boronic esters **7**. This would extend our strategy to a three-component decarboxylative conjunctive cross-coupling reaction, allowing rapid, convergent build-up of molecular complexity using abundant, readily available feedstock materials. Furthermore, the incorporation of the versatile boronic ester into the product would provide a valuable functional handle for further manipulation.[12,13] Herein, we report the first example of a metallaphotoredox-catalyzed decarboxylative conjunctive cross-coupling reaction between carboxylic acids, vinyl boronic esters and aryl iodides.

During our studies, we focused on the use of secondary α-amino acids as substrates because (i) they are readily available and would provide access to structurally complex alkyl boronic ester products; and (ii) we wished to address a limitation of previously reported metallaphotoredox-catalyzed conjunctive

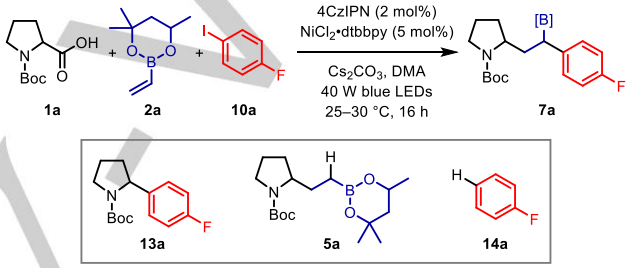
cross-couplings, which are mainly limited to reactions of tertiary alkyl radicals,[7] unless highly electrophilic conjunctive reagents are employed.[7b] This is because tertiary radicals do not readily undergo the competing nickel-catalyzed two-component coupling reactions whereas secondary radicals do. A proposed mechanism for the decarboxylative conjunctive cross-coupling is depicted in Scheme 2. Initial SET between the excited state photocatalyst (PC*) and the conjugate base of carboxylic acid **1a** generates a carboxyl radical that decarboxylates to give α-amino radical **8**. The nucleophilic radical **8** then adds to vinyl boronic ester **2** to form the stabilized α-boryl radical **3**. Concurrently, the nickel catalytic cycle begins by formation of aryl nickel(II) complex **9** by oxidative addition of aryl halide **10** to the Ni(0) catalyst. Interception of radical **3** by **9**, followed by reductive elimination of the resulting nickel(III) species **11**, provides the desired conjunctive cross-coupled product **7**. Final SET between the reduced state of the photocatalyst ($PC^{\bullet-}$) and nickel(I) complex **12** completes the two catalytic cycles. We recognized two main challenges associated with the successful development of this conjunctive cross-coupling: (i) the rate of addition of radical **8** to the vinyl boronic ester **2** must be faster than addition of **8** to the nickel(II) complex **9** in order to avoid formation of the two-component coupling product **13**, which is challenging because alkyl radicals add to vinyl boronic esters with a rate >20 times lower than that for addition to acrylates;[14] and (ii) the rate of reaction of α-boryl radical **3** with **9** must be faster than SET between **3** and the reduced photocatalyst ($PC^{\bullet-}$), which is necessary to prevent the formation of Giese product **5**.[9]



Scheme 2. Proposed mechanism.

Our investigations began with the reaction of Boc-Pro-OH **1a**, hexylene glycol vinyl boronic ester **2a**, and 4-fluoroiodobenzene (**10a**) (Table 1). We were delighted to find that using 2 mol% of the organic photocatalyst, 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN), 5 mol% $NiCl_2$•glyme and 6 mol% 4,4′-di-*tert*-butyl-2,2′-dipyridyl (dtbbpy) in combination with Cs_2CO_3 gave the desired conjunctive cross-coupled product in 79% yield, outcompeting direct two-component coupling of **1a** and **10a**, Giese hydroalkylation and protodehalogenation of the aryl iodide limiting reagent (entry 1). The use of pinacol boronic ester (vinyl-Bpin) in place of **2a** resulted in lower yield of **7a** and an increase in formation of Giese product **5a** (entry 2). The corresponding aryl bromide led to a dramatic decrease in yield, with increased amounts of Giese product **5a** suggesting inefficient nickel catalysis (entry 3). Lowering the equivalents of vinyl boronic ester **2a** resulted in a reduced yield of **7a** due to competitive formation of two-component coupling product **13a** (entry 4); however we were surprised to still see good selectivity for **7a** (compare entries 1 and 4, **7a**:**13a** = 6:1 vs. 3:1). Further evaluation of catalyst loading and solvent provided no improvement in efficiency (entries 5–8). Finally control experiments confirmed the necessity of the two catalysts, base, and light (entries 9–12).

Table 1. Optimization studies.



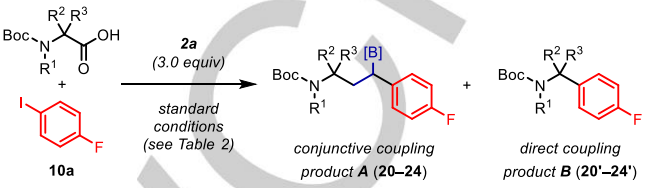
Entry	variation from above conditions	% yield[a]				
		7a	**13a**	**5a**[b]	**14a**	**10a**
1	none	79	13	8	7	0
2	vinyl-Bpin instead of **2a**	69	7	17	17	0
3	ArBr instead of **10a**	5	2	52	11	58
4	1.5 equiv of **2a**	67	22	8	11	0
5	10 mol% $NiCl_2$•dtbbpy	75	13	8	12	0
6	DMF as solvent	70	13	11	16	0
7	DMSO as solvent	23	5	15	27	18
8	MeCN as solvent	38	12	17	20	19
9	no photocatalyst	0	0	0	7	69
10	no nickel/dtbbpy	0	0	11	58	0
11	no base	0	0	0	2	75
12	no light	0	0	0	0	89

All reactions were carried out with **1a** (0.12 mmol), **2a** (0.30 mmol), **10a** (0.10 mmol), $NiCl_2$•glyme (5 mol%), dtbbpy (6 mol%), and Cs_2CO_3 (1.3 equiv) in DMA (4 mL). [a] Determined by ^{19}F NMR using hexafluorobenzene as an internal standard. [b] Determined by GC using 1,2,4-trimethoxybenzene as an internal standard. DMA = *N*,*N*-dimethylacetamide.

With the optimal reaction conditions in hand we next explored the scope of the conjunctive cross-coupling reaction with respect to the carboxylic acid substrate (Table 2, top). For isolation of the products, we found that partial instability of the benzylic hexylene glycol boronic esters resulted in diminished yields (64% for **7a**) and that in situ oxidation with H_2O_2 allowed isolation of the corresponding alcohols in high yield (76% for **7a**). A range of cyclic secondary α-amino acids, including those with different ring sizes and carbamate protecting groups, gave the corresponding three-component coupled products in moderate to

high yields (**15**–**18**). A cyclic tertiary amino acid also reacted with good efficiency (**19**). In addition, primary, secondary and tertiary acyclic α-amino acids were found to be suitable substrates (**21**–**30**), and a range of functional groups were tolerated under the mild conditions. In general, we found that lower yields were obtained with substrates containing an NH group, however, *N*-methylation resulted in improved yields. Alternatively, a phthalimide protecting group could be used, providing **26** in moderate yield. The reaction was not only limited to α-amino acids, as α-oxy acids also gave the corresponding products in modest to high yield, including Trolox (**31**), a vitamin E analogue, bezafibrate (**32**), a fibrate-drug, and clofibric acid (**33**), a herbicide. The successful application of these substrates exemplifies the potential to rapidly incorporate molecular complexity at a late stage into biologically important molecules.

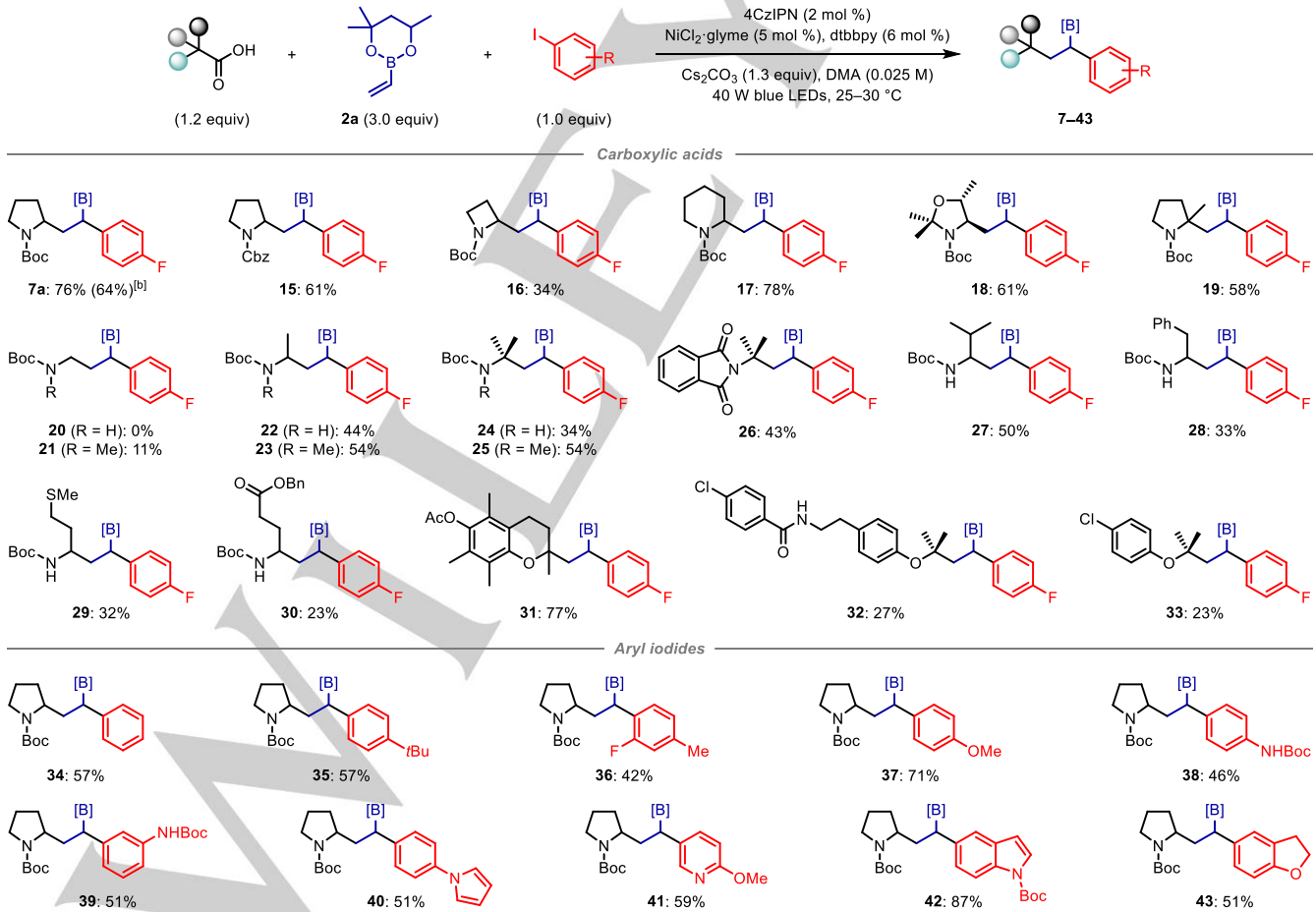
Given the known application of α-amino acids in metallaphotoredox-catalyzed two-compound cross-couplings,[5a] and the previous reliance on tertiary alkyl radical precursors in conjunctive cross-couplings,[7,13] we were intrigued by the unexpected high selectivity for conjunctive cross-coupling in our system so proceeded to investigate the effect of sterics on the reaction outcome (Scheme 3). The use of the primary α-amino acid, Boc-Gly-OH gave none of the desired product **20**, instead forming only the two-component cross-coupled product **20′**. Interestingly, methylating the nitrogen of Boc-Gly-OH (forming Boc-*N*-Me-Gly-OH) resulted in an 11% yield of product **21**, increasing the selectivity for conjunctive cross-coupling from <5:95 to 24:76. Selectivity was switched in favor of conjunctive cross-coupling upon changing to secondary α-amino acids due to increased steric hindrance around the putative carbon-centered radical, with Boc-Ala-OH providing a 67:33 ratio of **22**:**22′**. The beneficial effect of *N*-methylation was also observed with alanine as Boc-*N*-Me-Ala-OH provided **23** with >95:5 selectivity over the direct coupling product **23′** (entry 4). As expected, the tertiary



substrate	products	product ratio (*A*:*B*)
Boc-Gly-OH (R^1, R^2, R^3 = H)	**20′**	<5:95
Boc-Me-Gly-OH (R^1 = Me; R^2, R^3 = H)	**21** and **21′**	24:76
Boc-Ala-OH (R^1, R^2 = H; R^3 = Me)	**22** and **22′**	67:33
Boc-Me-Ala-OH (R^1, R^2 = Me; R^3 = H)	**23**	>95:5
Boc-Aib-OH (R^1 = H; R^2, R^3 = Me)	**24**	>95:5

Scheme 3. Effect of sterics on product selectivity.

Table 2. Decarboxylative conjunctive cross-coupling scope.[a]

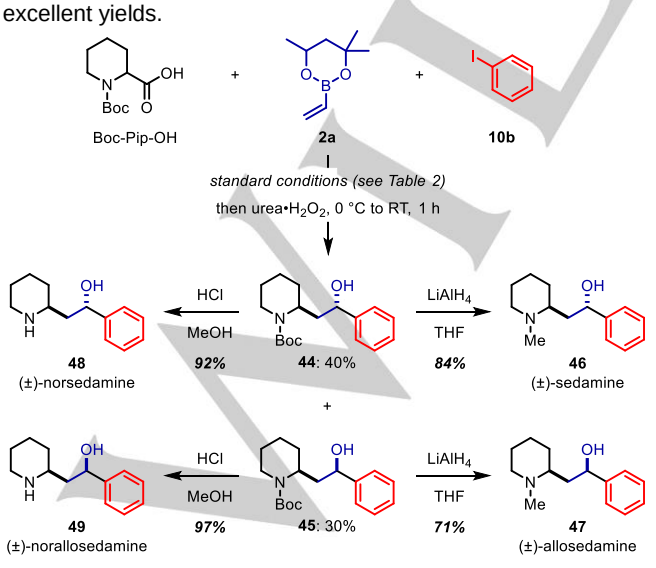


[a] Reactions were carried out on a 0.30 mmol scale with irradiation times of between 16 and 48 h. See Supporting Information for exact experimental procedures. Yields are of isolated products after oxidation with urea hydrogen peroxide (3.0 equiv). Products **7a**, **15**–**19**, **22**–**31**, and **34**–**43** were formed as mixtures of diastereomers with diastereomeric ratios of between 50:50 and 66:34. [b] Yield of isolated boronic ester on 0.10 mmol scale.

carboxylic acid, Boc-Aib-OH provided complete selectivity for conjunctive cross-coupled product **24**. The importance of sterics for promoting conjunctive cross-coupling was further highlighted by the unsuccessful reaction of simple unhindered secondary aliphatic carboxylic acids.[15]

Next, we explored the use of different aryl iodides (Table 2, bottom). A wide range of electron-rich aryl iodides could be effectively coupled to give the desired conjunctive cross-coupled products (**34**–**43**)**.** In addition to alkyl substituents, *ortho*-fluoro (**35**) and *para*-methoxy (**36**) groups were tolerated. Various iodoaniline derivatives also reacted in good yields, providing *para*- and *meta*-carbamates **38** and **39**, and pyrrole **40**. Heterocyclic iodides were also successful coupling partners, including pyridines,[16] indoles and benzodihydrofurans, giving products **41**–**43** in good to excellent yields. Unfortunately, although electron-deficient aryl iodides were competent coupling partners, the boronic ester products proved unstable to protodeboronation under the reaction conditions.[15] Furthermore, extension of this decarboxylative conjunctive cross-coupling to other Michael acceptors, such as acrylates, proved unsuccessful due to the facile generation of Giese hydroalkylation products.[15] Presumably, the success of the vinyl boronic esters is due to a slower rate of reduction of the α-boryl radical **3** by the reduced photocatalyst ($PC^{\bullet-}$), compared to the corresponding α-carboxyl radical (–1.25 V[9] vs. –0.6 V[17] respectively), which allows it to be intercepted by the nickel(II) complex **9**.

In order to demonstrate the utility of this methodology, we applied it in two-step syntheses of several *sedum* alkaloids, including sedamine (**46**)**,** which shows potential in the treatment of cognitive disorders, and allosedamine (**47**), which is used in the treatment of respiratory illnesses (Scheme 4).[18] These alkaloids contain the ubiquitous 1,3-aminoalcohol motif, which is easily generated using this methodology. Conducting the decarboxylative conjunctive cross-coupling with Boc-Pip-OH, vinyl boronic ester **2a** and iodobenzene **10b**, followed by in situ oxidation with H_2O_2 provided the separable diastereomeric γ-amino alcohols **44** and **45** in 70% combined yield. Subsequent reduction of the Boc-group with $LiAlH_4$ provided (±)-sedamine (**46**) and (±)-allosedamine (**47**) in 84% and 71% yield from **44** and **45**, respectively. Alternatively, Boc-deprotection with methanolic HCl gave (±)-norsedamine (**48**) and (±)-norallosedamine (**49**) in excellent yields.



Scheme 4. Application to the synthesis of *sedum* alkaloids.

In conclusion, a metallaphotoredox-catalyzed decarboxylative conjunctive cross-coupling of vinyl boronic esters with carboxylic acids and aryl iodides has been developed for the synthesis of complex alkyl boronic esters from feedstock materials. The unexpectedly high selectivity for conjunctive cross-coupling over direct two-component coupling in reactions of secondary α-amino acids is distinct from many previously reported radical-mediated conjunctive cross-couplings, which rely heavily on the use of tertiary alkyl radical precursors.[7,13] This allowed the reaction to be applied to a wide range α-amino acids, and the synthetic utility of the method was highlighted in concise syntheses of four *sedum* alkaloids.

Acknowledgements

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Keywords: metallaphotoredox catalysis • decarboxylative cross-coupling • conjunctive cross-coupling • alkyl boronic esters • carboxylic acids

[1] For selected reviews on multicomponent reactions, see: a) J. E. Biggs-Houck, A. Younai, J. T. Shaw, *Curr. Opin. Chem. Biol.* **2010**, *14*, 371; b) R. C. Cioc, E. Ruijter, R. V. A. Orru, *Green Chem.* **2014**, *16*, 2958; c) S. Zhi, X. Ma, W. Zhang, *Org. Biomol. Chem.* **2019**, *17*, 7632.

[2] J. Derosa, V. T. Tran, V. A. van der Puyl, K. M. Engle, *Aldrichimica Acta* **2018**, *51*, 21.

[3] T. Patra, D. Maiti, *Chem. Eur. J.* **2017**, *23*, 7382.

[4] a) J. Twilton, C. Le, P. Zhang, M. H. Shaw, R. W. Evans, D. W. C. MacMillan, *Nat. Rev. Chem.* **2017**, *1*, 0052; b) J. A. Milligan, J. P. Phelan, S. O. Badir, G. A. Molander, *Angew. Chem. Int. Ed.* **2019**, *58*, 6152; *Angew. Chem.* **2019**, *131*, 6212.

[5] For selected examples, see: a) Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle, D. W. C. MacMillan, *Science* **2014**, *345*, 437; b) A. Noble, S. J. McCarver, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2015**, *137*, 624; c) Z. Zuo, H. Cong, W. Li, J. Choi, G. C. Fu, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2016**, *138*, 1832; d) C. P. Johnston, R. T. Smith, S. Allmendinger, D. W. C. MacMillan, *Nature* **2016**, *536*, 322.

[6] A single report of decarboxylative three-component conjunctive cross-coupling of alkynes was recently reported, see: C. Zhu, H. Yue, B. Maity, I. Atodiresei, L. Cavallo, M. Rueping, *Nat. Catal.* **2019**, *2*, 678.

[7] a) L. Guo, H.-Y. Tu, S. Zhu, L. Chu, *Org. Lett.* **2019**, *21*, 4771; b) A. García-Domínguez, R. Mondal, C. Nevado, *Angew. Chem. Int. Ed.* **2019**, *58*, 12286; *Angew. Chem.* **2019**, *131*, 12414; For a metallaphotoredox-catalyzed conjunctive cross-coupling of alkynes, see: c) L. Guo, F. Song, S. Zhu, H. Li, L. Chu, *Nat. Commun.* **2018**, *9*, 4543.

[8] During the preparation of this manuscript, Molander reported a metallaphotoredox-catalyzed conjunctive cross-coupling of vinyl boronic esters using readily available potassium alkyl trifluoroborate salts, see: M. W. Campbell, J. S. Compton, C. B. Kelly, G. A. Molander, *J. Am. Chem. Soc.* **2019**, *141*, 20069.

[9] a) A. Noble, R. S. Mega, D. Pflästerer, E. L. Myers, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2018**, *57*, 2155; *Angew. Chem.* **2018**, *130*, 2177; For a review of radical additions to alkenylboron compounds, see: b) G. J. Lovinger, J. P. Morken, *Eur. J. Org. Chem.* **2019**, DOI: 10.1002/ejoc.201901600.

[10] C. Shu, R. S. Mega, B. J. Andreassen, A. Noble, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2018**, *57*, 15430; *Angew. Chem.* **2018**, *130*, 15656.

[11] a) J. Schmidt, J. Choi, A. T. Liu, M. Slusarczyk, G. C. Fu, *Science* **2016**, *354*, 1265; b) S.-Z. Sun, R. Martin, *Angew. Chem. Int. Ed.* **2018**, *57*, 3622; *Angew. Chem.* **2018**, *130*, 3684.

[12] C. Sandford, V. K. Aggarwal, *Chem. Commun.* **2017**, *53*, 5481.

[13] For a conjunctive cross-coupling of vinyl boronic esters using organozinc reagents, see: M. Chierchia, P. Xu, G. J. Lovinger, J. P. Morken, *Angew. Chem. Int. Ed.* **2019**, *58*, 14245; *Angew. Chem.* **2019**, *131*, 14383.

[14] N. Guennouni, L. Lhermitte, S. Cochard, B. Carboni, *Tetrahedron* **1995**, *51*, 6999.

[15] See Supporting Information for details.

[16] For the formation of product **41**, the electron-donating 2-methoxy substituent on the pyridine ring was required to avoid protodeboronation of the boronic ester product.

[17] N. Bortolamei, A. A. Isse, A. Gennaro, *Electrochim. Acta* **2010**, *55*, 8312.

[18] S. G. Davies, A. M. Fletcher, P. M. Roberts, A. D. Smith, *Tetrahedron* **2009**, *65*, 10192.

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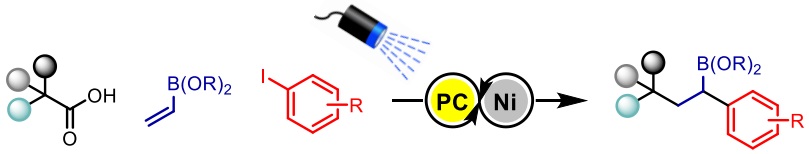

♦ *Feedstock materials* ♦ *One-step to molecular complexity* ♦ *Modular construction*

One-step to molecular complexity: A decarboxylative conjunctive cross-coupling of carboxylic acids, vinyl boronic esters and aryl iodides is described. The reaction proceeds under mild metallaphotoredox conditions and utilizes readily available feedstock materials, namely secondary α-amino acids, to access highly functionalized benzylic boronic esters in a single step.